

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix 1. Mutation Nomenclature

Mutations are described using the Human Genome Variation Society (HGVS) nomenclature (<http://www.hgvs.org/mutnomen>) in which the nucleotide numbering is from the A of the ATG translation initiator codon. For deletions or insertions the most 3' position possible is arbitrarily assigned to have been changed. The description of mutations is given at the genomic level (using cDNA reference sequences NM\_007294.3 / *BRCA1* and NM\_000059 / *BRCA2*). BIC nomenclature also is presented for common variants that are familiar to many researchers and clinicians by their BIC designation (<http://research.nhgri.nih.gov/bic>). For BIC nomenclature, cDNA sequences are used as reference sequence (Genbank: U14680 / *BRCA1* and NM\_000059.1 / *BRCA2*). The nucleotide numbering begins at nucleotide 1 of the cDNA sequence. For deletions or insertions the most 3' position possible was arbitrarily assigned to represent the mutation position in this nomenclature.

## eAppendix 2. Penetrance Estimation

Let RR be the relative risk/hazard estimated from our data, and  $p(Y=0|X)$  be the survivor function. Then

$$P(Y=0 | X=1) = \exp [-\Lambda_0 (\tau) \text{RR}]$$

$$P(Y=0 | X=0) = \exp[-\Lambda_0 (\tau)]$$

Where  $\Lambda_0 (\tau)$  is the hazard function. Therefore,

$$P(Y=0 | X=1) = P(Y=0 | X=0)^{\text{RR}} \quad (1)$$

In order to estimate the penetrance  $P(Y=1|X=0)$ ,

$$P(Y=1) = P(Y=1|X=1) P(X=1) + P(Y=1|X=0)P(X=0) \quad (2)$$

Substituting Equation (1) into Equation (2), we have

$$P(Y=1) = (1-P(Y=0|X=0)^{\text{RR}}) P(X=1) + (1-P(Y=0|X=0)^{\text{RR}}) P(X=0) \quad (3)$$

$P(Y=1)$  is available from the BOADICEA model<sup>1</sup>, and the values of  $P(X=1)$  and  $P(X=0)$  are available from the CIMBA data set. In this example, we use mutation prevalence estimates from the UK EMBRACE study sample as the reference population (<http://www.cancerresearchuk.org/about-cancer/trials/a-study-of-people-who-have-faulty-breast-cancer-genes>). We solve Equation (3) numerically for  $P(Y=0|X=0)$ . Then  $P(Y=1|X=1)$  can be computed as  $1 - P(Y=0|X=0)^{\text{RR}}$ .

To compute 95% confidence intervals (95%CI), we assume the value of the variance of RR is known, and  $\beta$  is the estimate of  $P(Y=0 | X=0)$ . The variance of these two estimators is  $\sigma^2_{\text{RR}}$  and  $\sigma^2_{\beta}$ , respectively. To compute the variance of  $1-P(Y=0 | X=0)^{\text{RR}}$ , we apply the multivariate delta method such that

$$\begin{aligned} g(\text{RR}, \beta) &= P(Y=1 | X=1) \\ &= 1 - P(Y=0 | X=0)^{\text{RR}} \\ &= 1 - \beta^{\text{RR}}. \end{aligned}$$

Then

$$\frac{dg(RR, \beta)}{d(RR)} = -RR \beta^{RR-1}$$

$$\frac{dg(RR, \beta)}{d(\beta)} = -\beta^{RR} \ln(RR)$$

Assuming the two estimators have no correlation, the variance of  $1 - \beta^{RR}$  is

$$\begin{aligned} \text{var}(1 - \beta^{RR}) &= [-RR \beta^{RR-1} \quad -\beta^{RR} \ln(RR)] \begin{bmatrix} \sigma_{RR}^2 & 0 \\ 0 & \sigma_{\beta}^2 \end{bmatrix} \times \begin{bmatrix} -RR \beta^{RR-1} \\ -\beta^{RR} \ln(RR) \end{bmatrix} \\ &= (RR \beta^{RR-1})^2 \sigma_{RR}^2 + (\beta^{RR} \ln(RR))^2 \sigma_{\beta}^2 \end{aligned}$$

We compute  $RR$ ,  $\beta$ ,  $\sigma_{RR}^2$ ,  $\sigma_{\beta}^2$  using the data available to us as described in the main text.

This provides us with  $1 - \beta^{RR}$ , which can be used to compute a 95% CI as

$$1 - \beta^{RR} \pm 1.96 \sqrt{\text{var}(1 - \beta^{RR})}$$

## Reference

1. Antoniou AC, Cunningham AP, Peto J, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancers: updates and extensions. *Br J Cancer*. 2008;98(8):1457-1466.

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**eTable 1. Study Sample - Numbers of Individuals with *BRCA1* or *BRCA2* Mutations by Center and Cancer Status**

Center ID	Study Name	Country	<i>BRCA1</i>					<i>BRCA2</i>					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total <i>BRCA1</i>	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total <i>BRCA2</i>	
BCFR	Breast Cancer Family Registry	USA/Canada/Australia	383	35	29	221	668	295	13	9	213	530	1,198
BFOCC	Baltic Familial Breast Ovarian Cancer Consortium	Latvia/Lithuania	87	91	18	52	248	7	2	0	1	10	258
BIDMC	Beth Israel Deaconess Medical Center	USA	32	4	0	1	37	22	3	0	28	53	90
BMBSA	BRCA-gene mutations and breast cancer in South African women	South Africa	43	8	8	17	76	98	12	3	43	156	232
BRICOH	Beckman Research Institute of the City of Hope	USA	80	28	7	140	255	53	9	4	90	156	411
CBCS	Rigshospitalet	Denmark	121	62	19	33	235	82	14	3	19	118	353
CNIO	Spanish National Cancer Centre	Spain	122	28	28	100	278	189	20	7	143	359	637
COH	City of Hope Cancer Center	USA	125	17	12	81	235	121	5	2	54	182	417
CONSTIT TEAM	CONsorzio Studi Italiani sui Tumori Ereditari Alla Mammella	Italy	372	165	86	258	881	348	33	28	160	569	1,450
DEMO-KRITOS	National Center for Scientific Research "Demokritos"	Greece	115	39	14	26	194	14	0	0	3	17	211
DFCI	Dana Farber Cancer Institute	USA	66	11	8	78	163	54	4	2	79	139	302
DKFZ	German Cancer Research Center	Germany/Pakistan/Colombia	148	15	7	85	255	41	5	2	35	83	338
DNA HEBON	Genen Omgeving studie van de	Netherlands	553	99	47	621	1,320	280	40	20	501	841	2,161

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	
EMBRACE	werkgroep Hereditair Borstkanker Onderzoek Nederland Epidemiological Study of Familial Breast Cancer	UK	529	90	64	539	1,222	445	55	21	520	1,041	2,263
FCCC	Fox Chase Cancer Center	USA	50	16	6	51	123	45	13	4	50	112	235
GC-HBOC	German Familial Breast Group	Germany	1,030	200	108	468	1,806	579	47	26	312	964	2,770
GEMO	Genetic Modifiers of cancer risk in BRCA1/2 mutation carriers	France/ USA	895	223	141	559	1,818	684	56	23	274	1,037	2,855
GEORGE- TOWN	Georgetown University	USA	27	3	2	19	51	17	3	0	21	41	92
GOG	Gynecologic Oncology Group	USA	227	0	0	240	467	161	0	0	160	321	788
HCSC	Hospital Clinico San Carlos	Spain	66	21	12	78	177	77	9	3	74	163	340
HEBCS	Helsinki Breast Cancer Study	Finland	47	10	11	28	96	64	6	7	51	128	224
HRBCP	Study of Genetic Mutations in Breast and Ovarian Cancer patients in Hong Kong and Asia	Hong Kong	21	5	5	13	44	41	0	1	19	61	105
HUNBOCS	Molecular Genetic Studies of Breast- and Ovarian Cancer in Hungary	Hungary	105	23	6	54	188	36	5	0	21	62	250
HVH	University Hospital Vall d'Hebron	Spain	34	6	4	26	70	39	3	1	25	68	138
ICO	Institut Català d'Oncologia	Spain	81	27	11	72	191	118	16	9	91	234	425
IHCC	International Hereditary Cancer	Poland	638	143	28	673	1,482	14	8	1	12	35	1,517

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	
ILUH	Centre Iceland Landspítali - University Hospital	Iceland	5	0	3	0	8	145	2	10	33	190	198
INHERIT	Interdisciplinary HEalth Research Internal Team BREast Cancer susceptibility	Canada (Quebec)	48	13	4	53	118	51	5	3	58	117	235
IOVHBOCS	Istituto Oncologico Veneto	Italy	70	50	17	28	165	98	14	8	31	151	316
IPOBCS	Portuguese Oncology Institute- Porto Breast Cancer Study	Portugal	28	14	5	50	97	66	2	2	53	123	220
KCONFAB	Kathleen Cunningham Consortium for Research into Familial Breast Cancer	Australia/ New Zealand	363	44	29	290	726	301	21	9	253	584	1,310
KOHBRA	Korean Hereditary Breast Cancer Study	Korea	99	1	6	26	132	153	1	2	62	218	350
MAGIC	Modifiers and Genetics in Cancer	USA	35	11	2	66	114	32	4	1	52	89	203
MAYO	Mayo Clinic	USA	159	33	16	160	368	100	14	5	88	207	575
MCGILL	McGill University	Canada (Quebec)	25	2	2	30	59	17	1	0	25	43	102
MDAND	MD Anderson Cancer Center	USA	103	22	5	54	184	0	0	0	0	0	184
MOD-SQUAD	Modifier Study of Quantitative Effects on Disease	Czech Republic/ Belgium	185	43	23	45	296	93	10	5	35	143	439
MSKCC	Memorial Sloane Kettering Cancer Center	USA	201	29	15	117	362	148	23	2	86	259	621
MUV	General Hospital Vienna	Austria	214	37	28	185	464	126	6	7	86	225	689

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	
NCI	National Cancer Institute	USA	40	10	4	98	152	18	5	1	51	75	227
NNPIO	N.N. Petrov Institute of Oncology	Russia	89	20	6	14	129	3	0	0	0	3	132
OCGN	Ontario Cancer Genetics Network	Canada	73	33	14	115	235	69	21	1	90	181	416
OSU CCG	The Ohio State University Comprehensive Cancer Center	USA	66	8	7	47	128	55	11	2	37	105	233
OUH	Odense University Hospital	Denmark	147	60	18	201	426	134	16	7	164	321	747
PBCS	Università di Pisa	Italy	47	16	12	23	98	42	2	0	14	58	156
SEABASS	South East Asian Breast Cancer Association Study	Malaysia/Singapore	41	7	3	6	57	32	0	1	4	37	94
SMC	Sheba Medical Centre	Israel	301	133	21	340	795	167	42	7	179	395	1,190
SWE-BRCA	Swedish Breast Cancer Study	Sweden	215	97	43	212	567	85	20	2	68	175	742
UCHICAGO	University of Chicago	USA	36	3	6	44	89	39	6	1	22	68	157
UCLA	University of California Los Angeles	USA	42	6	3	59	110	26	3	0	45	74	184
UCSF	University of California San Francisco	USA	44	24	3	49	120	46	7	3	38	94	214
UKGRFOCR	UK and Gilda Radner Familial Ovarian Cancer Registries	UK/USA	25	103	11	45	184	4	21	2	12	39	223
UPENN	University of Pennsylvania	USA	229	47	30	148	454	147	16	9	123	295	749
VFCTG	Victorian Familial Cancer Trials Group	Australia	71	20	11	6	108	42	12	2	13	69	177
WCP	Women's Cancer Program at	USA	54	62	13	127	256	17	16	4	45	82	338

Center ID	Study Name	Country	BRCA1					BRCA2					TOTAL
			Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA1	Breast Cancer Only	Ovarian Cancer Only	Breast and Ovarian Cancer	No Cancer	Total BRCA2	
	Cedars-Sinai Medical Center												
TOTAL			9,052	2,317	1,041	7,171	19,581	6,180	682	272	4,766	11,900	31,481

**eTable 2. Bins and Risks Used to Define Ovarian and Breast Cancer Cluster Regions (Depicted in Figure 2): *BRCA1***

Bin	Putative Region*	Bin Starting Nucleotide	Bin Ending Nucleotide	N	N (Breast Cancer)	HR, 95% CI (Breast Cancer)	N (Ovarian Cancer)	HR, 95%CI (Ovarian Cancer)	Ratio (HR-Breast: HR-Ovarian) (95%CI)	P-Value
1		1	67	151	84	1.17 (0.93,1.48)	23	0.90 (0.60,1.33)	1.31 (0.82-2.09)	0.265
2		68	69	2328	1036	0.89 (0.82,0.96)	392	0.94 (0.83,1.07)	0.94 (0.81-1.10)	0.456
3		70	178	243	146	1.24 (1.04,1.48)	54	0.97 (0.73,1.27)	1.28 (0.94-1.75)	0.116
4	BCCR1	179	181	984	546	1.11 (1.01,1.22)	118	0.74 (0.61,0.89)	<b>1.50 (1.21-1.85)</b>	<b>&lt;0.001</b>
5	BCCR1	182	505	403	239	1.17 (1.03,1.34)	62	0.87 (0.67,1.12)	<b>1.35 (1.00-1.82)</b>	<b>0.048</b>
6		506	927	407	218	0.98 (0.85,1.13)	75	0.94 (0.75,1.18)	1.05 (0.80-1.38)	0.750
7		928	1116	398	198	0.89 (0.77,1.02)	81	0.96 (0.77,1.20)	0.92 (0.70-1.22)	0.573
8		1117	1379	370	167	1.00 (0.86,1.17)	55	1.07 (0.82,1.40)	0.94 (0.68-1.29)	0.686
9	OCCR	1380	1674	377	165	0.81 (0.69,0.95)	82	1.31 (1.05,1.63)	<b>0.62 (0.47-0.82)</b>	<b>0.001</b>
10		1675	1892	399	208	0.91 (0.80,1.05)	90	1.10 (0.89,1.36)	0.83 (0.64-1.08)	0.172
11	OCCR	1893	2071	390	168	0.84 (0.72,0.99)	76	1.20 (0.94,1.54)	<b>0.70 (0.52-0.94)</b>	<b>0.019</b>
12	OCCR	2072	2338	396	180	0.78 (0.67,0.91)	70	1.04 (0.81,1.33)	<b>0.75 (0.56-0.99)</b>	<b>0.049</b>
13	OCCR	2339	2475	450	210	0.88 (0.77,1.00)	94	1.21 (1.00,1.48)	<b>0.72 (0.56-0.93)</b>	<b>0.010</b>
14		2476	2685	448	208	0.89 (0.77,1.03)	73	1.05 (0.83,1.33)	0.85 (0.64-1.13)	0.251
15	OCCR	2686	3013	399	175	0.84 (0.73,0.98)	91	1.30 (1.05,1.61)	<b>0.65 (0.50-0.85)</b>	<b>0.001</b>
16	OCCR	3014	3254	378	164	0.79 (0.68,0.92)	96	1.23 (1.00,1.52)	<b>0.64 (0.48-0.85)</b>	<b>0.002</b>
17		3255	3331	393	180	0.90 (0.77,1.05)	78	1.12 (0.89,1.41)	0.80 (0.61-1.07)	0.131
18		3332	3482	373	179	0.86 (0.75,1.00)	84	1.13 (0.90,1.42)	0.76 (0.58-1.01)	0.059
19		3483	3661	398	196	0.85 (0.74,0.98)	62	0.84 (0.64,1.10)	1.02 (0.74-1.40)	0.910
20		3662	3753	384	187	0.93 (0.80,1.07)	68	1.13 (0.91,1.41)	0.82 (0.63-1.08)	0.152
21		3754	3770	406	210	1.00 (0.87,1.15)	88	1.14 (0.93,1.41)	0.88 (0.67-1.14)	0.326
22		3771	4016	350	148	0.93 (0.79,1.11)	67	0.95 (0.73,1.25)	0.98 (0.70-1.36)	0.892
23	OCCR	4017	4062	321	118	0.65 (0.53,0.78)	101	1.11 (0.87,1.41)	<b>0.58 (0.42-0.81)</b>	<b>0.001</b>
24		4063	4167	419	217	1.20 (1.04,1.38)	67	1.15 (0.92,1.43)	1.04 (0.79-1.37)	0.761
25		4168	4327	513	281	1.18 (1.04,1.34)	82	0.99 (0.79,1.24)	1.20 (0.92-1.56)	0.186
26	BCCR2	4328	4945	417	252	1.16 (1.02,1.32)	67	0.86 (0.68,1.11)	<b>1.34 (1.01-1.78)</b>	<b>0.042</b>
27		4946	5123	486	270	1.00 (0.88,1.13)	90	0.93 (0.75,1.16)	1.07 (0.83-1.39)	0.605
28		5124	5260	361	224	1.17 (1.02,1.34)	67	0.90 (0.70,1.16)	1.30 (0.97-1.74)	0.076
29	BCCR2	5261	5266	3052	1666	1.20 (1.13,1.27)	459	0.92 (0.83,1.02)	<b>1.30 (1.14-1.48)</b>	<b>&lt;0.001</b>
30	BCCR2	5267	5563	482	289	1.30 (1.15,1.47)	65	0.79 (0.62,1.01)	<b>1.65 (1.25-2.17)</b>	<b>&lt;0.001</b>

\*BCCR: breast cancer cluster region, OCCR: ovarian cancer cluster region

**eTable 3. Bins and Risks Used to Define Ovarian and Breast Cancer Cluster Regions (Depicted in Figure 3): *BRCA2***

Bin	Putative Region*	Bin Starting Nucleotide	Bin Ending Nucleotide	N	N (Breast Cancer)	HR, 95%CI (Breast Cancer)	N (Ovarian Cancer)	HR, 95% CI (Ovarian Cancer)	Ratio (HR-Breast: HR-Ovarian)	P-Value
1	BCCR1	1	596	663	391	1.17 (1.04,1.32)	33	0.68 (0.43,1.08)	<b>1.72 (1.06-2.78)</b>	<b>0.028</b>
2		597	771	586	381	1.11 (0.96,1.29)	43	1.13 (0.76,1.68)	0.98 (0.64-1.51)	0.931
3	BCCR1'	772	1806	623	364	1.08 (0.97,1.20)	31	0.66 (0.46,0.96)	<b>1.63 (1.11-2.40)</b>	<b>0.014</b>
4		1807	2786	573	310	0.96 (0.85,1.08)	39	0.83 (0.60,1.14)	1.16 (0.82-1.66)	0.399
5		2787	3248	611	332	0.98 (0.88,1.10)	42	0.88 (0.64,1.21)	1.12 (0.79-1.59)	0.524
6	OCCR1	3249	3847	590	285	0.78 (0.69,0.88)	61	1.38 (1.07,1.78)	<b>0.57 (0.42-0.76)</b>	<b>0.000</b>
7	OCCR1	3848	4478	535	264	0.91 (0.80,1.03)	57	1.38 (1.05,1.80)	<b>0.66 (0.49-0.89)</b>	<b>0.007</b>
8	OCCR1	4479	5238	555	251	0.80 (0.70,0.90)	57	1.19 (0.89,1.59)	<b>0.67 (0.48-0.93)</b>	<b>0.017</b>
9	OCCR1	5239	5681	523	280	0.98 (0.87,1.10)	56	1.54 (1.15,2.04)	<b>0.64 (0.47-0.87)</b>	<b>0.005</b>
10		5682	5945	611	357	1.09 (0.98,1.22)	43	0.87 (0.63,1.20)	1.26 (0.89-1.77)	0.188
11	OCCR1	5946	5946	1341	579	0.74 (0.64,0.86)	155	1.27 (0.99,1.63)	<b>0.58 (0.45-0.76)</b>	<b>0.000</b>
12		5947	6275	612	322	1.07 (0.96,1.20)	41	0.80 (0.58,1.09)	1.35 (0.96-1.90)	0.090
13		6276	6644	542	301	0.95 (0.85,1.07)	43	0.99 (0.73,1.34)	0.97 (0.69-1.35)	0.841
14	OCCR2	6645	7471	582	302	0.85 (0.74,0.97)	64	1.49 (1.12,1.97)	<b>0.57 (0.41-0.80)</b>	<b>0.001</b>
15		7472	7933	571	320	1.09 (0.96,1.23)	47	1.03 (0.73,1.45)	1.06 (0.74-1.52)	0.759
16	BCCR2	7934	8535	752	455	1.19 (1.07,1.33)	43	0.50 (0.34,0.74)	<b>2.37 (1.56-3.59)</b>	<b>0.000</b>
17	BCCR2	8536	8904	507	302	1.27 (1.11,1.44)	31	0.60 (0.39,0.92)	<b>2.12 (1.34-3.35)</b>	<b>0.001</b>
18		8905	9118	565	345	1.22 (1.08,1.39)	34	0.93 (0.60,1.46)	1.31 (0.82-2.11)	0.264
19		9119	9925	558	311	1.07 (0.96,1.20)	34	0.73 (0.52,1.04)	1.46 (0.99-2.14)	0.054